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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,751	07/06/2001	Keith D. Allen	R-386	4567

7590 03/24/2004

DELTAGEN, INC.
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Menlo Park, CA 94025

EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,751	ALLEN ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Non-Final Rejection

Claims 21-25 are pending.

Applicant's traversal, the addition of claims 21-25 and the cancellation of claims 17-20 in paper filed on 10/31/03 is acknowledged and considered.

This application contains sequence disclosures that are encompassed by the definition for nucleotide sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements for Patent Applications Containing Nucleotide Sequence Disclosures.

The sequences GDSGGP and IIGG are listed in the specification (page 1, line 27) but are not listed in the CRF.

Response to Arguments

Applicant's arguments, filed 10/31/03, with respect to the 101 rejection have been fully considered and are persuasive. The rejection of claim 19 has been withdrawn because of the cancellation of the claims. However, upon further consideration, a new ground(s) of rejection is made in view of the new claims.

Applicant's arguments, filed 10/31/03, with respect to the 112 first paragraph rejection have been fully considered and are persuasive. The rejection of claims 17-20 has been

withdrawn because of the cancellation of the claims. However, upon further consideration, a new ground(s) of rejection is made in view of the new claims.

Specification

The disclosure is objected to because of the following informalities: the status (e.g., pending, abandoned, patented US Patent No.) of US applications listed on page 10, line 24 and page 11, line 6 is missing.

Claim Objections

Claims 21, 23, and 24 are objected to because of the following informalities: the phrase "**wherein, where** the disruption is homozygous" on line 2 of claims 21 and 24 and line 9 of claim 23 is grammatically incorrect. Claims 22 and 25 are also objected to because the claims depend from claims 21 and 24, respectively.

Suggest removing either "wherein" or "where" from the phrase.

Appropriate correction is required.

Claim Rejections - 35 USC § 101 and 35 USC § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-25 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a substantial or well-established utility.

The specification discloses that a mouse gene encoding a new type of membrane bound serine protease containing a multi-domain structure was recently isolated and sequenced, SEQ ID NO: 1 (page 2). The specification further discloses disrupting the gene comprising SEQ ID NO: 1 in a mouse using a targeting construct (pages 51-52). No homozygous mutant mice were identified, whereas wild type and heterozygous mutant mice were present. Homozygous mutant mice were identified as embryos as late as E14.5 days (pages 51-52). The specification does not teach how the disruption affected the expression of the gene comprising SEQ ID NO: 1 in the homozygous embryo, e.g., reduced expression, increased expression, no expression of the serine protease gene comprising SEQ ID NO: 1. In addition, the specification does not disclose a phenotype for the heterozygous mutant mice. The specification further discloses measuring expression of an unspecified gene in organs of an unspecified animal (pages 52-53).

The specification contemplates identifying and characterizing serine protease enzymes, which can play a role in preventing, ameliorating or correcting dysfunction or diseases (page 3). The specification further contemplates methods of identifying agents capable of affecting a phenotype of a transgenic animal and methods of identifying agents having an effect on serine protease expression of function (page 4).

The claims are drawn a transgenic mouse whose genome comprises a disruption in a serine protease gene comprising SEQ ID NO: 1, wherein the disruption is heterozygous, and wherein, upon breeding with a second transgenic mouse whose genome comprises a disruption in

the serine protease gene comprising SEQ ID NO: 1, the transgenic mouse produces a transgenic mouse having a homozygous disruption in the serine protease gene comprising SEO ID NO: 1 and. The claims recite using the transgenic heterozygous mouse to produce a homozygous mouse exhibiting a lethality during embryonic development. At the time the invention was made, it was known that serine proteases are a large family of proteolytic enzymes (page 1). The as-filed specification provides no nexus between the 'association' of the transgenic homozygous mouse exhibiting a lethality during embryonic development produced by using the claimed mouse and a phenotype, disease, and/or disorder associated with an enzyme from the serine protease family.

The specification contemplates using a heterozygous mouse to produce a homozygous mouse (page 15) and, the specification does not specifically teach a use for the homozygous mutant embryo. The new claims recite using the claimed heterozygous transgenic mouse to produce a homozygous mouse exhibiting a lethality during embryonic development. Even though the claimed heterozygous mouse can be used to produce a homozygous mutant embryo, it would require further experimentation on the products made directly (e.g., homozygous mutant embryo) and/or indirectly (cells from the homozygous embryo) from the claimed transgenic heterozygous mouse to determine whether the products were involved in any disease, and then to determine what association with the disease means or how the homozygous mouse can be used. Consequently, the specification fails to teach a substantial use for the heterozygous mouse in this context. See In re Kirk, 376 F.2d 936, 153 USPQ 48 (CCPA 1967).

Furthermore, the specification contemplates using the heterozygous mouse in a screening assay *in vivo* or *in vitro*. The specification does not teach a phenotype for the claimed transgenic

heterozygous mouse. In view of the lack of a phenotype for the heterozygous transgenic mouse it would require one skilled in the art to compare the heterozygous with a mouse with a wild-type serine protease gene and determine if there is a phenotype for the heterozygous mouse compared to the wild type mouse. Then, one skilled in the art would have to determine how this phenotype is associated with a known disease or disorder associated with the phenotype observed. Furthermore, it would require experimentation on the products made indirectly (e.g., cells made from the heterozygous mouse) to observe whether the products were involved with any biological function associated with a serine protease in vitro, and then to determine how the observation relates to a disease or disorder and what the observation with the disorder or disease means. Consequently, the specification fails to teach a substantial use for the heterozygous mouse in this context.

With respect to using the homozygous mouse produced from the claimed transgenic mouse in any *in vivo* screening assay, the specification does not teach what to look for as a result of using the homozygous mouse in any *in vivo* assay. One skilled in the art would have to experiment on the invention to determine what results would be observed, and then to determine what such results would mean or how the results can be used. In addition, in view of the lethality at E12.5 to E14.5, one skilled in the art would have to experiment to determine the parameters for studying the embryo before the onset of the lethality. In absence of the specification teaching what to look for in the assays, the claimed invention lacks utility.

With respect to storing the phenotype associated with a disruption in the serine protease in a database (pages 15-16), it would require further experimentation on the homozygous mouse made from the claimed transgenic mouse to determine whether the lethality during embryonic

development was involved in any disease or disorder. In addition, it would require experimentation on the mouse to determine how the disruption affected the expression of the gene comprising SEQ ID NO: 1 in the homozygous mutant embryo.

With respect to using the homozygous mouse to study the protein encoded by SEQ ID NO: 1 and determine if it plays a role in preventing, ameliorating or correcting dysfunction or diseases, the specification provides no evidence that the lethality during embryonic development observed in the homozygous mutant embryo is involved in any activity associated with a serine protease. The specification provides no evidence that the homozygous mouse is associated with any known disease associated with a serine protease. It would require experimentation on the claimed invention/or products made directly or indirectly from the claimed mouse to determine whether the lethality during embryonic development were involved in any disease, and to then determine a use for the mouse in this context. In addition, in view of the lethality at E12.5 to E14.5, one skilled in the art would have to experiment to determine the parameters for studying the embryo before the onset of the lethality. Thus, the asserted utilities set forth above do not provide a benefit to the public in currently available form. See Ziegler, 992 F.2d at 1203, 26 USPQ2d 1600 (Fed. Cir. 1993).

The specification further contemplates comparing heterozygous mice and homozygous mice to normal, wild type mice to determine whether the disruption of the serine protease gene causes phenotypic changes, especially pathological changes (page 15). The specification does not disclose a phenotype for the heterozygous mouse. In addition, the specification does not disclose an association between embryonic lethality and a serine protease disease or disorder. In view of the lack of a phenotype for the heterozygous transgenic mouse it would require one

skilled in the art to compare the heterozygous with a mouse with a wild-type serine protease gene and determine if there is a phenotype for the heterozygous mouse compared to the wild type mouse. It would further require experimentation on the homozygous mouse to determine whether the lethality during embryonic development were involved in any disease, and to then determine a use for the mouse in this context. In view of the reasons set forth above, the claimed invention lacks utility.

Since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention. See also In Brenner v. Manson, 383 US 519, 148 USPQ 689 (1966). Also see REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS: www.uspto.gov/web/menu/utility.pdf.

Claims 21-25 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a well asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 21-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the

quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to a transgenic mouse whose genome has a disruption in a serine protease gene comprising SEQ ID NO: 1, wherein the disruption is heterozygous and wherein upon breeding with a second transgenic mouse whose genome comprises a disruption in the serine protease gene comprising SEQ ID NO: 1, the transgenic mouse produces a transgenic mouse having a homozygous disruption in the serine protease gene comprising SEQ ID NO: 1 and exhibiting a lethality during embryonic development. The invention lies in the field of transgenics.

The state of the art at the time application was filed for producing transgenic mice with a desired phenotype using a knock out method was considered unpredictable. The unpredictability of predicting a phenotype in transgenic mouse is supported by Linder (Lab Animal, Vol. 30, pages 34-39, 2001, cited on a previous PTO-892) who states "It is critical to remember that the observed phenotype is not always the direct result of the genetic alteration". Linder further states, "The expression of a phenotype in mice carrying an induced mutation may depend on a number of factors not readily apparent to the initial researcher nor to those using the model in subsequent studies (page 35)."

The art of record teaches the unpredictability of producing transgenic mouse with a desired phenotype. The individual gene of interest, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of genetically modified animals, which exhibit a particular phenotype. This observation is supported by Wall (Theriogenology, 1996, cited on a previous PTO-892) who states "Our understanding of essential

genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1997, cited on a previous PTO-892) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); e.g. specific promoters, presence or absence of introns, etc.

The specification recites, "the serine proteases are a large family of proteolytic enzymes that include the digestive enzymes, trypsin, and chymotrypsin, components of the complement cascade and of the blood-clotting cascade (page 1)." The as-filed specification defines a serine protease gene as the polynucleotide sequence set forth in SEQ ID NO: 1. The specification teaches that a mouse gene encoding a new type of membrane bound serine protease (epithin, SEQ ID NO: 1) was isolated and sequenced by Kim et al. (cited on a PTO-1449, Kim et al., 1999), see page 2 of the specification. Kim teaches that, "The sequence was shown to be highly expressed in a thymic epithelial nurse cell line." Kim further teaches that they suspect that epithin will target either an extracellular matrix or another membrane bound protein on the same or neighboring cells.

The specification provides prior art pertaining to the preparation of transgenic mice (pages 11-13 and 15-18). The specification teaches a method of generating a transgenic mouse comprising: 1) A vector comprising the cDNA encoding SEQ ID NO: 1 and 2) injected the vector into murine ES cells derived from 129/olaHsdby substrain (pages 51-52). Furthermore, the specification teaches that homozygous mutant embryos produced by the method died

between E12.5 and E14.5 (days) and no mutant mice were identified, whereas wild type and heterozygous mutant mice were present (pages 52-54).

The specification does not teach how the disruption affected the expression of the gene comprising SEQ ID NO: 1 in the homozygous embryo, e.g., reduced expression, increased expression, inhibited expression of SEQ ID NO: 1. The specification discloses measuring expression of an unspecified gene in organs of an unspecified animal (pages 52-53). In addition, the specification does not disclose a phenotype for the heterozygous mutant mice.

With respect to the mutant murine embryos produced in the working examples. The specification does not teach a genotype to confirm if the ES cells had the construct in the serine protease gene comprising SEQ ID NO: 1 or if the construct randomly integrated into the mouse's genome. The art of record teaches that random integration of a nucleic acid construct predominantly results when introducing a construct in ES cells. See US 6,689,610. The specification does not teach if the phenotype exhibited by the homozygous mutant murine embryo was expected when a serine protease comprising SEQ ID NO: 1 was disrupted using the construct taught in the working examples. Thus, in view of the lack of a genotype confirming a disruption in a serine protease comprising SEQ ID NO: 1 and lack of guidance for whether the phenotype for the homozygous was not the result of random integration of the nucleic acid construct into the mouse's genome, the specification lacks sufficient guidance and/or factual evidence for one skilled in the art to make the claimed transgenic mouse based on the teaching in the specification without further undue experimentation. One skilled in the art would have to make a transgenic mouse comprising a disrupting in a serine protease gene comprising SEQ ID

NO: 1 in a mouse and breed the mouse with another mouse and determine which litters would produce a homozygous embryo mutant with a lethality during embryonic development.

With respect to the claims and in view of the lack of guidance provided by the specification for one skilled in the art to make the claimed transgenic mouse, the claims are not considered enabled because the breadth of the claims encompasses making a transgenic mouse whose genome comprises any disruption in a serine protease gene comprising SEQ ID NO: 1 and breeding the mouse with a second transgenic mouse whose genome comprises any disruption in the same gene to produce a transgenic mouse having a homozygous disruption in the serine protease gene and exhibiting a lethality during embryonic development. The claims read on breeding mouse with the same disruption or a different disruption in a serine protease gene comprising SEQ ID NO: 1. The specification teaches making a murine embryo that exhibits lethality during embryonic development. See pages 52-54. However, the specification does not teach how to breed heterozygous mouse with different disruptions and produce a homozygous mouse exhibiting a lethality during embryonic development.

With respect to the term "disruption", the specification lacks guidance for one skilled in the art to practice the claimed invention using any disruption in the claimed serine protease gene. The specification teaches, "the disruption can alter the normal gene product by inhibiting its production partially or completely or by enhancing the normal gene product's activity." See page 7. The specification does not teach how the disruption affected the expression of the gene comprising SEQ ID NO: 1 in the homozygous embryo, e.g., inhibited expression, reduced expression, increased expression of the serine protease gene comprising SEQ ID NO: 1. The specification does not teach one skilled in the art how to make a genus of claimed transgenic

mouse because SEQ ID NO: 1 is cDNA and not genomic. The cDNA does not contain introns, 5' and 3' untranslated regions, untranscribed regions and regions between the promoter and the starting codon. In view of the lack of guidance provided by the specification for targeting regions not embraced by the cDNA, one skilled in the art would not be enabled to make a genus of constructs for disrupting a gene comprising SEQ ID NO: 1. In addition, the breadth of the term embraces embodiments not taught by the specification. The specification does not teach replacing the endogenous promoter of a gene comprising SEQ ID NO: 1, inserting a nucleotide sequence into an intron, etc. and making a genus of transgenic mouse that when breed with another mouse having a disruption in the a serine protease gene comprising SEQ ID NO: 1 could produce a homozygous mutant embryo having a lethality during embryonic development. In view of the breadth of the term "disruption", the lack of guidance in the specification for making a genus of transgenic mouse with a disruption in a gene comprising SEQ ID NO: 1, and the unpredictability in the art regarding transgenics, the specification does not provide sufficient guidance for one skilled in the art to make a genus of transgenic mouse with a disruption in a gene comprising SEQ ID NO: 1 to produce a homozygous mutant embryo having lethality during embryonic development.

In conclusion, in view of the quantity of experimentation necessary to make the claimed invention, the art of record teaching the unpredictability of making a transgenic mouse with a desired phenotype, and the lack of direction and/or sufficient guidance provided by the as-filed specification for one skilled in the art to make a genus of transgenic mouse with a disruption in a gene comprising SEQ ID NO: 1 as contemplated by the claimed invention, the claimed invention is not considered enabled.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Application No.: 09/900,751

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [X] 7. Other: The sequences GDSGGP and IIGG are listed in the specification (page 1, line 27) but are not listed in the CRF.

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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